A RANDOMIZED TRIAL COMPARING ACOMLA WITH CHOP-B

Philip M. Spiro

1983

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A RANDOMIZED TRIAL COMPARING DOXORUBICIN, CYCLOPHOSPHAMIDE, METHOTREXATE WITH LEUCOVORIN RESCUE, VINCRISTINE, AND CYTARABINE (ACOMLA), WITH DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISONE, AND BLEOMYCIN (CHOP-B) IN THE TREATMENT OF DIFFUSE HISTIOCYTIC LYMPHOMA

M.D. Thesis

Submitted to the Faculty

Yale University School of Medicine

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Medicine

Philip M. Spiro

May, 1983

ACKNOWLEDGEMENTS

I would like to thank the following individuals:

Doctors Ed Cadman and Mary Todd, for making this both a rewarding and painless experience.

Debbie Cibelli, Elizabeth "Isa" Hess, Stephen McCormick, and Mark Phillips, my housemates, for putting up with me during this period of relative trauma.

Jane Rosenthal, for her support, and for not telling me to get off the phone and back to work.

Finally, Meghan, Chani, Zooey, Spike "Heels" Jones, and Monster, for providing hours of free entertainment.

ABSTRACT

Forty eight patients with previously untreated diffuse histiocytic lymphoma (DHL) were treated prospectively with ACOMLA (hydroxydaunorubicin, cyclophosphamide, vincristine, methotrexate with leucovorin, and cytosine arabinoside) or CHOP-B (cylophosphamide, hydroxydaunorubicin, vincristine, prednisone, and bleomycin). Forty six of these patients were classified by the Lukes-Collins classification with the identification of 13 large cleaved follicular center cell, 7 large non-cleaved follicular center cell, 14 B-cell immunoblastic, 8 T-cell immunoblastic, and 4 large cell unclassified lymphomas. There was no difference in survival advantage between the two treatments. Overall complete response rate was 70% (with ACOMLA having a response rate of 68% and CHOP-B 71%). Of these, 4 of the ACOMLA patients and 3 of the CHOP-B patients have relapsed. Median follow-up time is 32 months. Median survival for all patients has not yet been reached. Drug toxicity was substantial with 3 drug related deaths. ACOMLA caused slightly more sepsis but the difference was not significant. Patients with follicular center cell (FCC) lymphomas had a significant survival advantage over patients with immunoblastic sarcomas ($p=0.01$). No difference in survival was found between the cleaved and non-cleaved FCC types. Age, sex, stage, site of involvement, or presence of symptoms were not significantly correlated with survival. Immunoblastic sarcomas (B and T cell types) appear to be more resistant to current chemotherapeutic regimens and may warrant more aggressive treatment.

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INTRODUCTION

The Non-Hodgkin's lymphomas (NHL) are a diverse group of neoplasms of the lymph nodes and lymphoid components of other tissues. The classification of these disorders has paralleled the scientific understanding of them and has been a source of controversy for many years. Ideally, the classification of any disease should be 1) easy to use, 2) reproducible, 3) scientifically accurate, and 4) prognostically and therapeutically significant. The production of such a scheme has been the theme of research done on these neoplasms since they were first described one hundred and fifty years ago.

This paper will present a brief history of the development of the classifications of non-Hodgkin's lymphomas as an introduction to a report of a study done at Yale between May, 1976 and April, 1982. This study is a prospective randomized trial of two different chemotherapeutic regimens for one of the most aggressive of the non-Hodgkin's lymphomas - diffuse histiocytic lymphoma. This trial was performed in such a way as to allow implications to be made on the ability of the Lukes-Collins classification (of the NHL) to identify subsets of diffuse histiocytic lymphoma that are refractory to treatment so that a more efficacious treatment can be designed for them.

GENERAL HISTORICAL BACKGROUND

Interest in the nature of lymphomas is generally considered to have begun in 1832, (though some will cite the work of Malpighi in 1661 or that of Morgagni in 1779), with a published report by the now-famous Thomas Hodgkin entitled "On some morbid appearances of the absorbent glands and the spleen" (1). In this report, Hodgkin presented the clinical features and pathologic appearance of seven patients with generalized lymphadenopathy and splenomegaly stating that "as far as could be ascertained from observation, or from what could be collected from the history of cases, this enlargement of the glands appeared to be a primitive affection of those bodies, rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed texture through the medium of their inferent vessels." Hodgkin also noted the condition of the spleen which was, in a few of the cases, "thickly pervaded with defined bodies of various sizes in structure resembling that of the diseased glands" and concluded that there was a "close connection between the derangement of the glands and that of the spleen". He believed that the involvement of the spleen was a secondary event to involvement of the lymph nodes "and on this account may not always have been produced, when that [derangement] of the glands or some other disease carried off the patient" (1).

This work by Hodgkin seems to have been largely ignored until the work of Sir Samuel Wilks. Wilks published a report of 15 patients with a similar disorder "thirteen of which resembled in all particulars...[those] which Mr Hodgkin first brought under the notice of the profession" (2). Wilks noticed

that this disease represented a distinct and separate pathological condition among all of the other afflictions of the lymph nodes and spleen. He also noticed the "remarkable anemia" and it is clear that he separated this disease from leukemia. Finally, in an act of chivalry, he preserved his predecessors name in history by naming the disorder "Hodgkin's" disease (3).

Before the work of Wilks, the German pathologist Virchow too had distinguished this disorder from leukemia, known at that time to be a disease of the peripheral blood and bone marrow, calling it "lymphosarcoma" (4). It remained until 1893 for Kundrat to develop histologic criteria for the diagnosis of lymphosarcoma, in order to distinguish it from "aleukemic leukemia" another term coined by Virchow, as well as from "lymphogranula", "lymphogranulomatosis" and a number of other synonyms for Hodgkin's disease (5). It remained, however, until 1902 for Dorothy Reed to describe the multinucleate giant cells (while she was still a medical student) which now bear her name, and develop histopathologic criteria for the diagnosis of Hodgkin's disease, which was felt to be a separate clinico-pathologic entity (3,6).

In 1926, Fox went back to the original material preserved by Hodgkin and, using the criteria developed by Reed and Sternberg, confirmed the diagnosis of Hodgkin's disease in only three of the original seven cases thus confirming the presence of a separate "non"-Hodgkin's lymphoma (7). Ewing, in 1928, described two kinds of "lymphosarcoma": "malignant lymphosarcoma" composed of smaller cells, and "reticulum cell sarcoma" composed of larger ones. He believed that these tumors arose from either reticulum cells or from lymphocytes in the germinal centers of lymph nodes (8). Two years later Roulet published

criteria for the diagnosis of "reticulum cell sarcoma" (9), and it was at this time that Brill described a group of lymphomas with "follicular" architecture which were radiosensitive and thus had a relatively benign prognosis.(10). This lymphoma came to be called "giant follicular lymphoma" or "Brill-Symmer's" disease after the work of N.E. Brill (11).

Thus, during the early part of this century pathologists generally divided the non-Hodgkin's lymphomas (NHL) into three groups based upon microscopic architecture; giant follicular lymphoma (or synonyms), lymphosarcoma, and reticulum cell sarcoma. While this loose classification represented the best understanding of the disease at that time (as well as the best in histologic technology), it proved to be of limited usefulness as it was difficult to reproduce, and, other than the relatively benign prognosis of the giant follicular lymphoma, provided little in the way of prognostic information (12,13).

Rappaport Classification

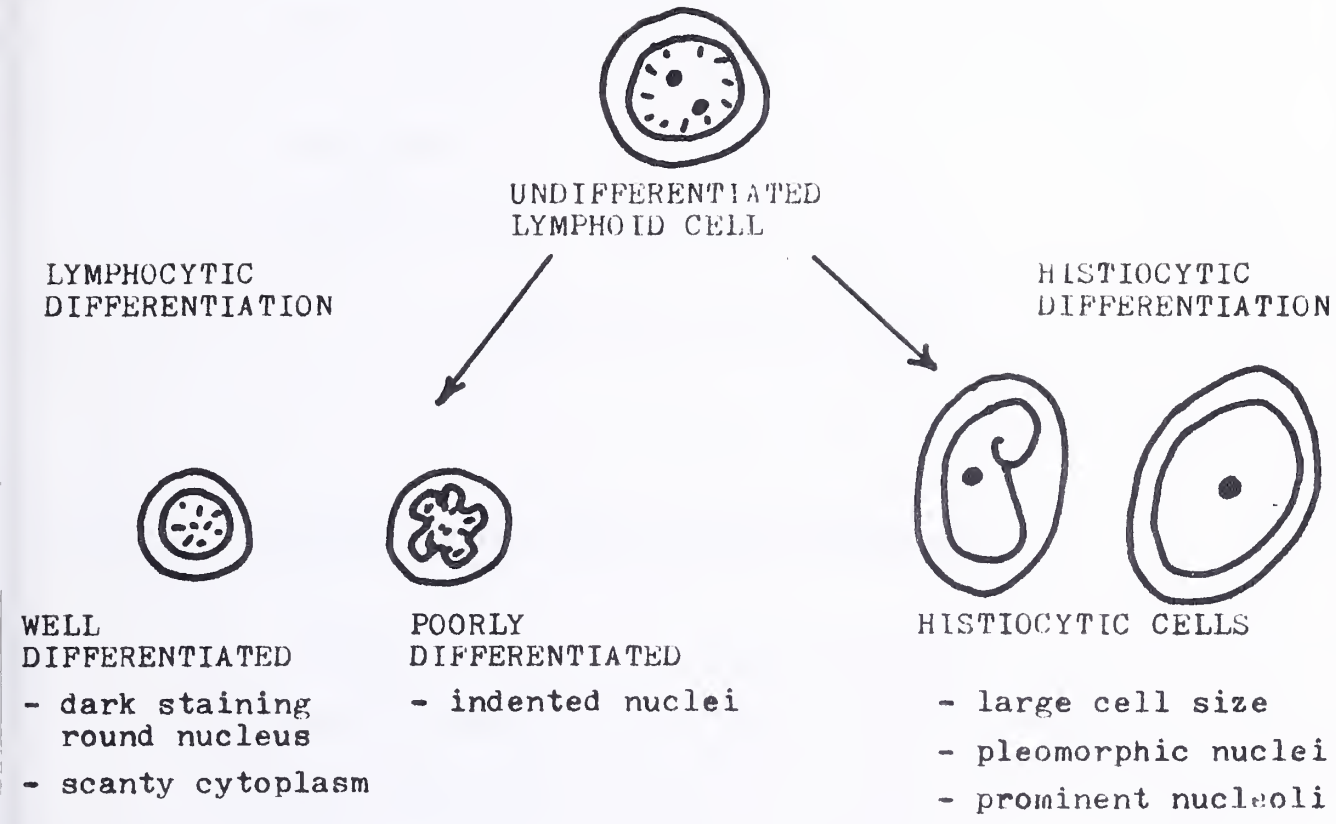
In spite of its limited usefulness, this classification scheme persisted until the early sixties when a classification developed by Rappaport, Winters, and Hicks, came into general use. These pathologists believed that a classification scheme should be based primarily on cytologic grounds (i.e. cell types) with a secondary emphasis on architecture (14). Their system, first published in 1956, further modified in 1966 and 1978 (15,16), proposed five groups of NHL (see table 1) divided by cell type (lymphocytic, histiocytic, or mixed lymphocytic-histiocytic) with each cell type showing two types of architecture; "nodular" where the lymphomatous cells are clustered around in discrete identifiable nodules or "diffuse" where the lymphomatous cells have spread to the point that they totally efface the underlying nodal structure. The lymphocytic groups are further modified by whether the cells are well or poorly differentiated. Table 2 shows the Rappaport classification in relation to the system that preceded it. The latest version of the Rappaport classification is shown in Table 3, and Figure 1 illustrates the essential morphologic characterizations.

Since its original publication in 1956, numerous studies have confirmed Rappaport's original assertion that, within each cell grouping, a lymphoma with a nodular (follicular) architecture confers a better prognosis than one with a diffuse pattern and that a lymphoma composed of lymphocytes, regardless of degree of differentiation, confers a better prognosis than a lymphoma composed of either mixed cells or histiocytes (14,16-21). Having thus been proven to provide valuable prognostic information, the Rappaport classification

gained wide acceptance and became the classification that was used in clinical trials world-wide.

However, during the late sixties and early seventies new information was being discovered about the structure, function, and maturation of lymphocytes that began to cast doubt upon the scientific accuracy of the Rappaport classification, which was based upon morphologic criteria alone, and did not include the new immunologic terminology. It was shown, for example, that the histiocytes of the Rappaport classification were not indeed "true" histiocytes but rather transformed B-lymphocytes which resembled histiocytes (22). In addition, studies were published that indicated that nodular lymphomas appeared to be uniformly composed of cells of B-lymphocyte origin (23). From these discoveries and others it became apparent to researchers at many centers that a classification scheme needed to be developed which would include modern concepts of the immune system. The search for the "conceptually relevant" classification scheme resulted in a veritable explosion of "new-improved" classifications which confounded clinician and researcher alike and left the mere student hopelessly lost. As the dust settled, however, it became clear that there remained no less than six classification schemes (excluding minor modifications) with the proponents of each claiming superiority over the others. These systems are (in alphabetical order): The British National Lymphoma Investigation (BNLI) classification, the Dorfman classification, the Lukes-Collins classification, the Kiel classification, the Rappaport classification, and the World Health Organization classification (24-27). While the details of the BNLI, Dorfman, Kiel, and WHO classifications are beyond the scope of this paper, the general outline and salient features of each will be given after a description of the Lukes-Collins classification.

Figure 1. Rappaport Classification



(adapted from J. Waldron handout 10/80)

Table 1. RAPPAPORT CLASSIFICATION (Original)

Nodular or Diffuse

Well-differentiated Lymphocytic

Poorly-differentiated Lymphocytic

Mixed Lymphocytic-Histiocytic

Histiocytic

Undifferentiated

(Adapted from Rappaport (14))

Table 2. RAPPAPORT CLASSIFICATION AND "OLD" TERMINOLOGY

Rappaport		Old Terminology
Nodular lymphomas (all cell types)	--------	Giant Follicular Lymphoma
Diffuse Lymphomas		
Lymphocytic	--------	Lymphosarcoma
Mixed	--------	Reticulum Cell Sarcoma
Histiocytic	--------	Reticulum Cell Sarcoma
Undifferentiated	-------	Reticulum Cell Sarcoma

(Adapted from Rappaport (14))

Table 3. RAPPAPORT CLASSIFICATION (UPDATED) WITH FREQUENCY OF OCCURENCE

Approx. % of total	
	NODULAR LYMPHOMAS
1	Lymphocytic, Well-differentiated
19	Lymphocytic, Poorly-differentiated
8	Mixed, Histiocytic and Lymphocytic
2	Histiocytic
	DIFFUSE LYMPHOMAS
4	Lymphocytic, Well-differentiated (± plasmacytoid features)
9	Lymphocytic, Poorly-differentiated (± plasmacytoid features)
8	Lymphoblastic, (± convolutions)
5	Mixed, Histiocytic and Lymphocytic
28	Histiocytic (± sclerosis)
2	Undifferentiated (Burkitt's and non-Burkitt's)
15	UNCLASSIFIED
100	

(Adapted from NCI sponsored study of NHL (23))

The Lukes-Collins Classification

The classification scheme for the NHL proposed by Lukes and Collins in 1974, subsequently modified in 1975 and 1976 (28-32), was one of the first to attempt to incorporate concepts of modern immunology. It is currently one of those most widely used in the U.S. but it is not without its critics. Lukes and Collins based their system on the premise that, since the malignant lymphoma are neoplasms of the immune system, they should be classified according to their B or T cell origins. They based their work on studies done in their own and in other's laboratories, which traced the normal development and transformation of lymphocytes under antigenic or mitogenic stimulation. Comparing this normal development with cytologic patterns in lymphomatous tissue, Lukes and Collins proposed that malignant lymphomas develop from a "block" or "swtich-on" (or derepression) in the normal transformation of lymphocytes (30).

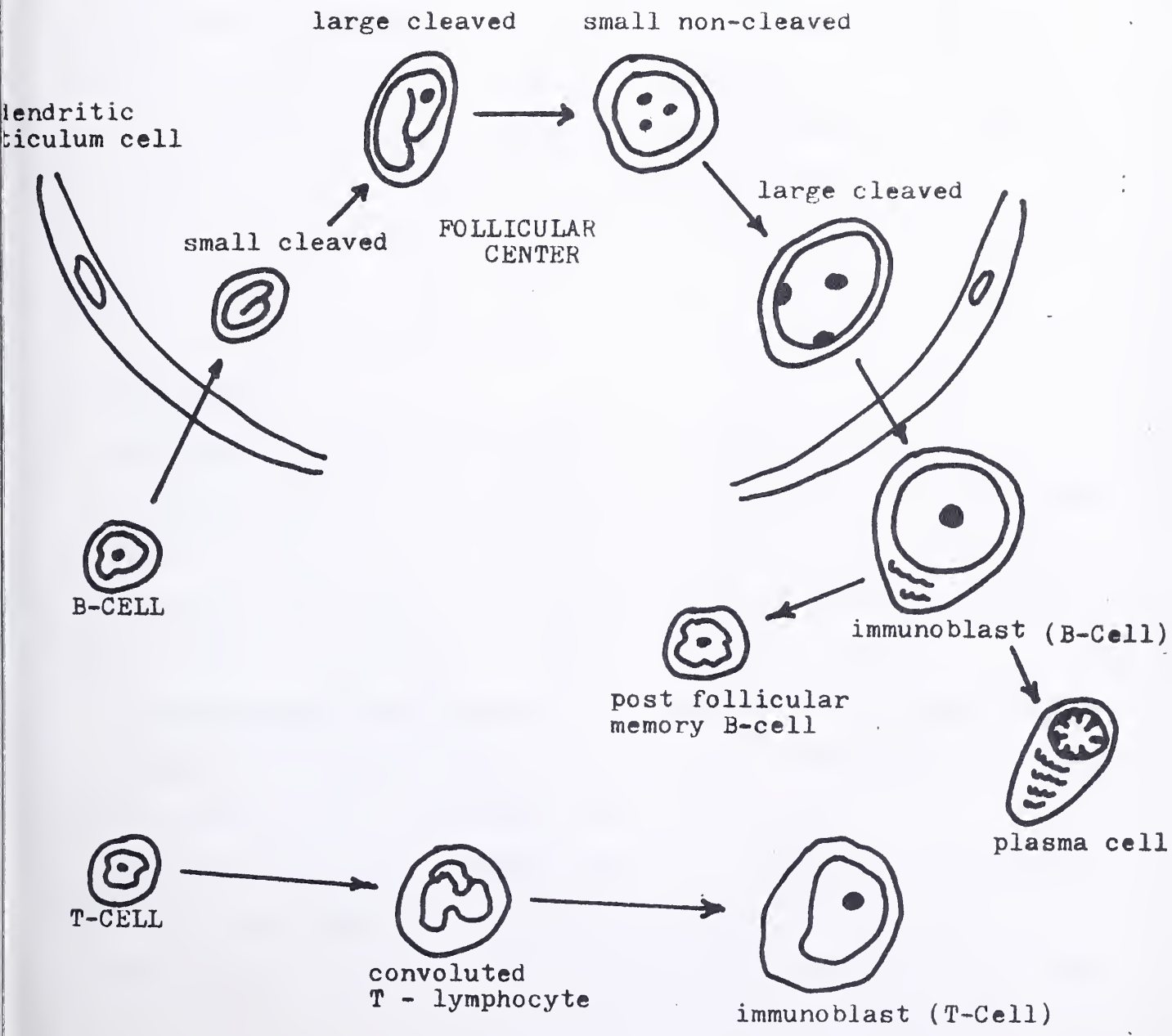
Tracing the normal transformation of a lymphocyte, either under antigenic or mitogenic stimulation, the cell can be seen to undergo four distinct phases of development which take place within the germinal follicle (also called the follicular center). First, the stimulated B-cell grows slightly and its nucleus develops a sharp infolding of the nuclear membrane which causes the nucleus to take on a bilobate or multilobate appearance. This infolding is called "cleavage" and is readily apparent under light microscopy with normal stains. At this stage, the cell is called a small cleaved follicular center cell (sclFCC). (It should be noted here that the word "follicular" is used in a different context than previously. Here "follicular" refers to a location

within a lymph node whereas previously, in the discussion of the Rappaport classification, "follicular" referred to a particular type of nodal architecture. It will be seen that "follicular" center cell lymphomas can take on a "follicular" architecture. As this has been known to confuse students of the lymphomas, the word "nodular" will be used instead of "follicular" when referring to architecture.) The cell then continues to grow, retaining its cleavage, to become, appropriately enough, a large cleaved follicular center cell (lclFCC).

At this point, the cell begins to show signs of mitotic activity, with mild affinity for pyronin stain (pyroninophilia) indicating an increase in protein synthesis, and the nuclear cleavage disappears. The cell is now called a small non-cleaved follicular center cell (sncFCC). Growth continues as the cell develops prominent nucleoli and the cell is now called a large non-cleaved follicular center cell (lncFCC), and can grow to as large as four times the size of a non-stimulated lymphcyte.

In this normal development it is apparent that the non-cleaved cells are the cells engaged in active replication while the cleaved cells represent their quiescent counterparts. Transformation of the stimulated lymphocyte continues but now takes place outside the follicle in the interfollicular area where the cell becomes an even more avid replicator as it undergoes transformation into an immunoblast. The cell becomes markedly pyroninophilic, develops a larger nucleus and many prominent nucleoli become visible. The immunoblasts proliferate into daughter cells which become either the antibody-producing plasma cells or small "memory" lymphocytes. These events in the normal B-cell transformation are depicted in Figure 2.

Figure 2. B and T Cell Transformation



(adapted from J. Waldron handout 10/80)

Small T-cell lymphocytes also have the potential of undergoing blast transformation but do so outside the germinal follicles in the parafollicular area and do not develop nuclear cleavage. Instead, as they pass from lymphocyte to immunoblast, they develop multiple nuclear lobulations which is called "chicken-footprinting" (33).

Believing then that lymphomatous development represents a block or derepression in the normal pattern of lymphocyte transformation, Lukes and Collins proposed nine different categories of lymphomas each corresponding to a block at a particular point of development. This is shown schematically with the lymphoma categories superimposed upon normal development in Figure 3. The formal Lukes-Collins classification is listed in Table 4 and will be described briefly.

B-Cell Lymphomas

Small B-cell Lymphoma: This lymphoma is composed of small, well-differentiated lymphocytes which appear like the unstimulated lymphocytes shown in Figure 2. The appearance of nodes from patients with small B-cell lymphomas is indistinguishable from those of patients with chronic lymphocytic leukemia (CLL) and indeed this disease often develops a leukemic component.

Plasmacytoid Lymphocytic Lymphoma: This lymphoma has a similar appearance to the small B-cell lymphoma but is believed to arise from a block at a different point and the cells contain plasmacyte features.

Follicular Center Cell Lymphomas: Composed of transformed B-cells with a follicular center origin, these lymphomas contain all variants of the follicular center cell (FCC); cleaved and non-cleaved, small and large. They

can be found with or without sclerosis. It is important to stress that Lukes and Collins place no significance on the nodular or diffuse nature of a FCC lymphoma. It is felt that the nodular forms of the FCC lymphomas merely represent the disease caught at an earlier stage before it has grown enough to efface the normal nodal architecture and become "diffuse" in appearance. FCC lymphomas are found which contain mixed cleaved and non-cleaved cells but Lukes and Collins do not have a category for a "mixed" cleaved-non-cleaved lymphoma. Instead, a FCC lymphoma is defined as non-cleaved if the node is "focally dominated by non-cleaved cells or the number exceeds 25% throughout" (31).

Immunoblastic Sarcoma (B-Cell Type): These lymphomas are composed of large non-cleaved cells, which are larger and have a more pyroninophilic cytoplasm than the large non-cleaved cells of the follicular center. They represent lymphomas of the fully transformed lymphocyte or immunoblast.

T-Cell Lymphomas

Small T-Cell Lymphoma: The small T-cell lymphoma is the T-cell counterpart of the small B-cell lymphoma. It, too, is associated with CLL. Morphologically it is similar to the B-cell lymphoma but has features by which it may be distinguished (34).

Sezary Syndrome - Mycosis Fungoides: Included here for completeness, these disorders have been proven to be of T-cell origin. They are, however, lymphomatous disorders confined to the skin and have a very different natural history than the other lymphomas discussed here. They will not be dealt with further.

Convoluted Lymphocyte: These lymphomas are composed of partially transformed T-lymphocytes which display the lobulation referred to as "chicken footprinting". They are easily confused with small cleaved FCC but can be differentiated by the presence of these lobulations. Convoluted lymphocyte lymphomas are commonly associated with a thymic mass and leukemic transformation.

Immunoblastic Sarcoma (T-Cell Type): The T-cell counterpart of the B-cell immunoblastic sarcoma, this lymphoma is a pleomorphic diffuse lymphoma with commonly a mixture of small and transformed lymphocytes. Nuclear irregularity is common as is a pale cytoplasm. The mean tumor cell size varies significantly from one case to another. Some of the T-immunoblastic sarcomas would be classified as Rappaport "histiocytic" lymphomas while others would be included in the mixed cell category (33,34).

Histiocytic Lymphomas: Unlike the Rappaport classification which identifies a larger number of "histiocytic" lymphomas, in the Lukes-Collins classification a lymphoma of "true" histiocytes is rare, occurring in one of Lukes and Collins' early studies only in one case of three hundred reviewed. Identified by their large size in the Rappaport classification, most "histiocytic" lymphomas turn out to be composed of large FCC or of immunoblasts (see Table 5). The prognostic significance of this will be discussed later.

Unidentified (U-Cell)

Lukes and Collins deemed a lymphoma to be a U-cell lymphoma when it lacked any surface markers by which it could be identified. The U-cell group, according to them, is "...hypothetical and provides a group for those

proliferations of lymphocytes that prove to have no discriminating cell markers detectable" (35). It essentially provides a "wastebasket" category and has been the object of some criticsm.

Unclassifiable

The "unclassifiable" group "...allows categorization of those processes that are technically unsatisfactory for precise cytologic classification but are sufficient for identification of the process as lymphomatous" (32). In the recent study by the NCI, 37% of routinely prepared slides were found to be "unclassifiable" by the Lukes-Collins system whereas the "unclassifiable" category for the other classification systems ranged from 15-30% (24).

Table 4. LUKES AND COLLINS CLASSIFICATION

T-CELL TYPES

Small Lymphocytic

Sezary-Mycosis Fungoides

Convoluted Lymphocytic

Immunoblastic Sarcoma of T-Cells

B-CELL TYPES

Small Lymphocytic

Plasmacytoid Lymphocytic

Follicular Center Cell, small cleaved*

Follicular Center Cell, large cleaved*

Follicular Center Cell, small non-cleaved*

Follicular Center Cell, large non-cleaved*

Immunoblastic Sarcoma of B-Cells

Histiocytic

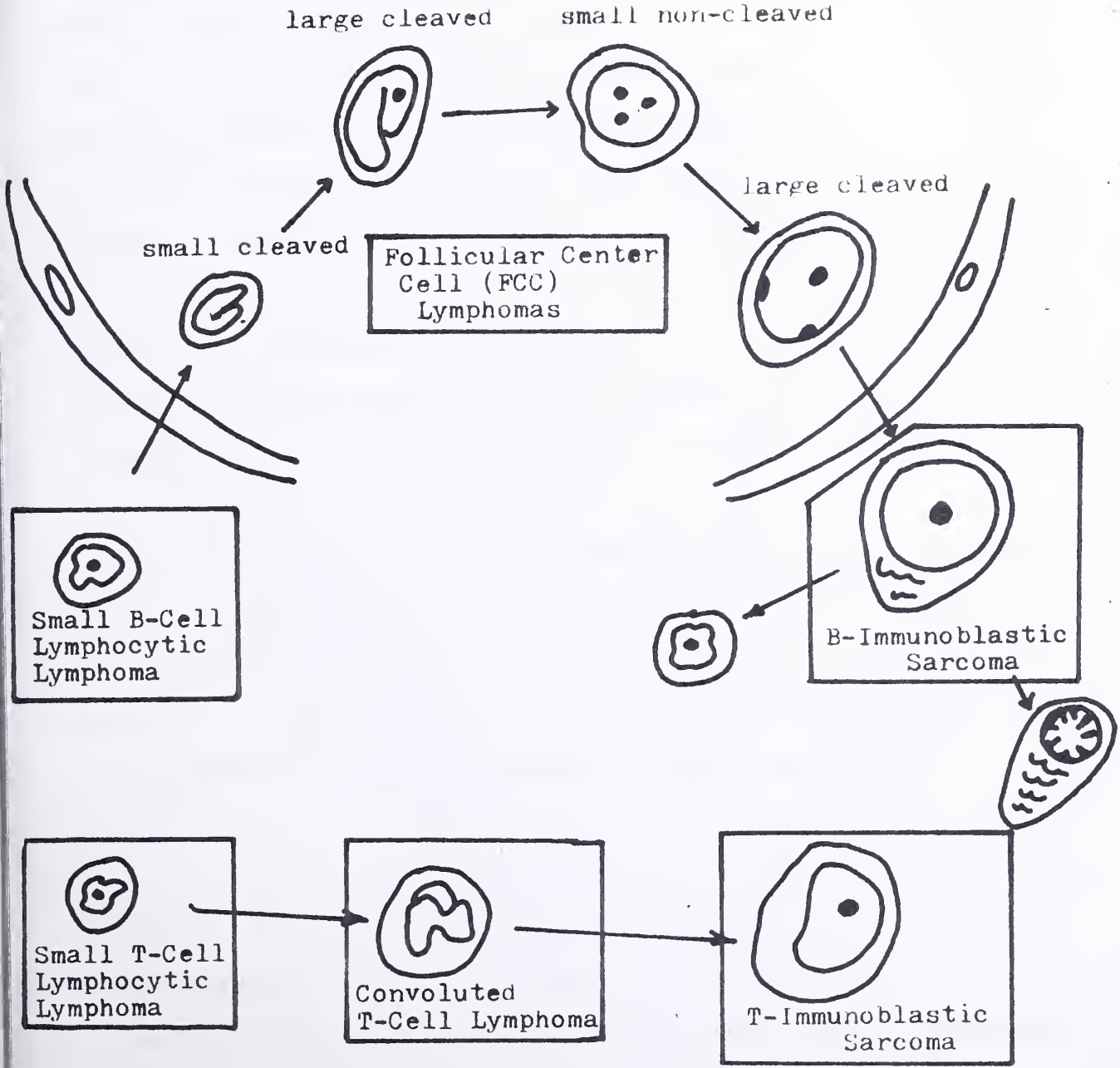
UNDEFINED

UNCLASSIFIED

*may be nodular, nodular and diffuse or diffuse, with or without sclerosis

(adapted from NCI sponsored study of NHL (24))

Figure 3. Lukes-Collins Classification:
Relation to normal transformation



(adapted from J. Waldron handout 10/80)

Prognostic Significance of Lukes-Collins Classification

Since one of the aims of a classification system is to provide some information about prognosis, the value of a system must be questioned, no matter how "scientifically accurate" or "conceptually relevant" it is, if it does not provide this information. This has been one of the more controversial points concerning the Lukes-Collins classification. Based as it is on presumed "blocks" or "switch-ons" in the path of normal lymphocyte transformation, it is tempting to assume that as one progresses from lymphomas composed of small non-transformed B-cells, which are mitotically inactive in their normal state, to lymphomas composed of immunoblasts, which in their normal state are poised ready to produce daughter cells, there would be a trend toward more aggressive neoplasms (32). Generally, this has been proven to be the case. Small B-cell lymphomas have a better prognosis than FCC lymphomas which, as a group (including large and small cells), have a better prognosis than immunoblastic sarcomas. (35).

There has been, however, some disagreement over the prognosis of the large cell groups: large FCC cleaved and non-cleaved, and the immunoblastic sarcomas (both B and T cell origin). Most studies indicate that the prognosis for the immunoblastic sarcomas is worse than that of the large cell FCC lymphomas (27, 31,35-38) although this is not a universal finding. Garvin et.al. (26) in a 22 year retrospective review, found that there was no significant difference between the FCC and the immunoblastic sarcomas, although there appeared to be a trend toward a better prognosis for the FCC lymphomas. This study, however, was a retrospective review where the patients received heterogeneous therapy and experienced generally poor survival. There seems to be more disagreement

over the prognosis of the other two large cell groups, the FCC large cleaved and the FCC large non-cleaved. One study by Strauchen et.al. (36) analyzed a series of 66 patients prospectively treated with either C-MOPP or BACOP (see section on treatment for an explanation of these acronyms). Their conclusion was that the large cleaved FCC had a better prognosis than the large non-cleaved FCC group ($p < 0.01$). This conclusion is supported by a prospective study by Stein (38) and a retrospective review by Barcos et.al. (45). Nathwani et. al. reported in 1978 (28) a retrospective review of 202 cases of DHL in which the large cleaved FCC lymphomas had a better prognosis. However, more recently they reported another series of 162 cases in which they found no difference in survival between any of the Lukes-Collins subtypes of the DHL (64). Armitage reported a series of patients (n=31) uniformly treated with CHOP in which the patients with large non-cleaved lymphomas did better than patients with large cleaved ones (37). Garvin's (26) retrospective study noted no difference between the two groups.

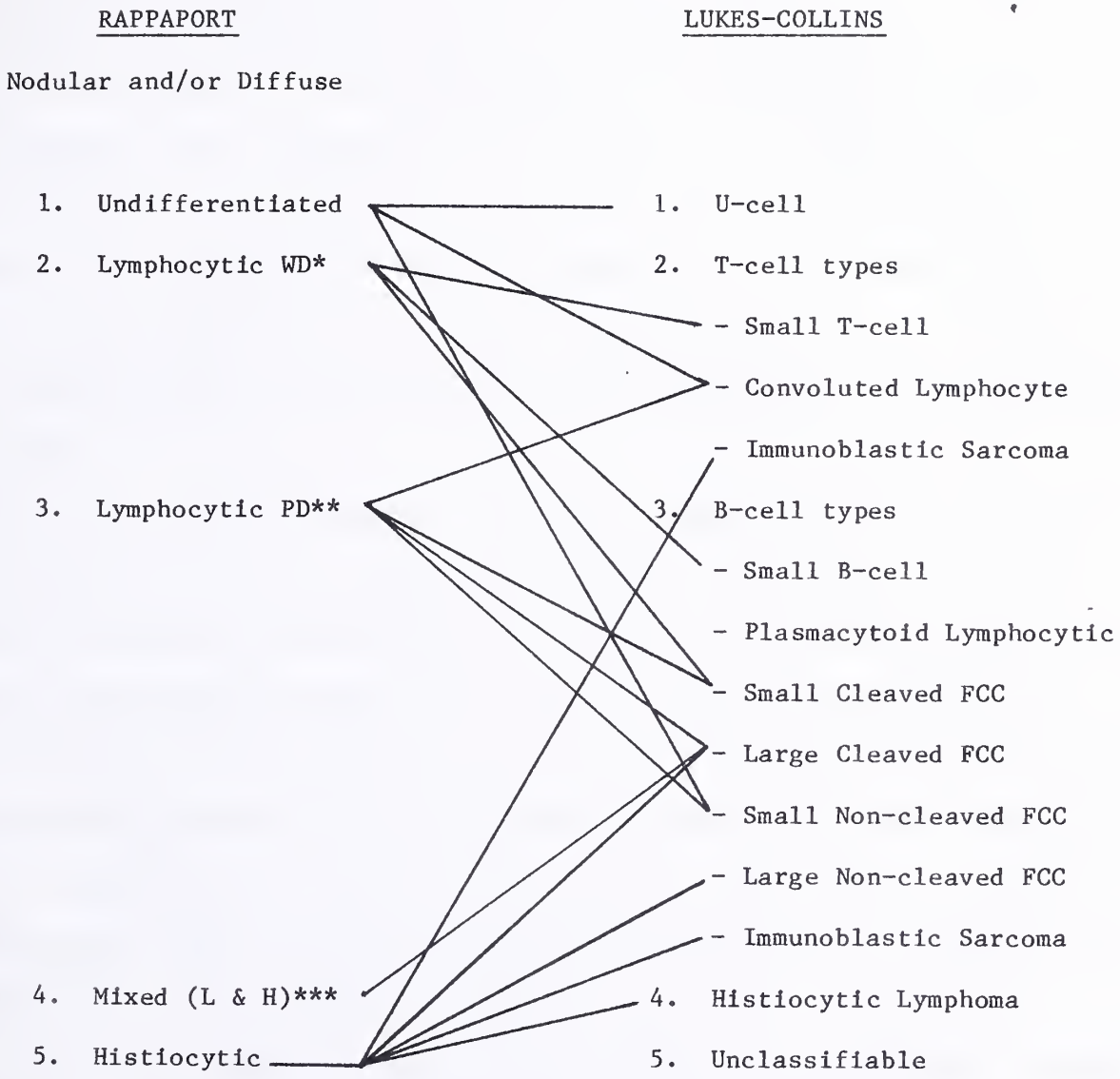
Comparison of Rappaport and Lukes-Collins Classifications

Table 5 shows the rough correlations between the Rappaport and Lukes-Collins classifications. The most obvious difference between the two is the fact that the former groups the lymphomas around cell type and architecture while the latter groups them around their immunologic origin. While architecture (nodular vs. diffuse) has been shown to be of prognostic significance in numerous studies, Lukes and Collins have not emphasized architecture because it is not relevant in light of modern discoveries in

immunology. As it was stated before, Lukes and Collins believe that nodular and diffuse lymphomas do not represent different clinical entities but rather reflect, within a given cell type, different stages of the same disease, with nodular lymphomas representing the early stages of the disease before the lymphomatous cells have spread and effaced the nodal architecture.

The second major difference between the two classifications is in the area of the "histiocytic" lymphoma. The Rappaport classification essentially defines the histiocyte by its large size. The Lukes-Collins classification, on the other hand, stresses the relative rarity of "true" histiocytic lymphomas and divides the Rappaport histiocytic lymphomas into five subgroups (see Table 5): lc1FCC, LncFCC, Immunoblastic sarcoma (both B and T cell derived), and "true" histiocytic lymphoma.

Table 5. COMPARISON OF LUKES-COLLINS AND RAPPAPORT CLASSIFICATIONS



* Well Differentiated

** Poorly Differentiated

*** Lymphocytic/Histiocytic

(Adapted from Lukes and Collins (30))

Criticism of the Lukes-Collins Classification

While Lukes and Collins have been widely praised for having introduced modern understanding of lymphoid physiology into a classification scheme for the lymphomas, their classification is not without its critics. In a well-cited study of the NHL comparing the Lukes-Collins classification with the Rappaport classification, the authors (Rappaport being among them) criticized the LCC along a number of lines. They reviewed a series of 202 cases of NHL and classified them according to both systems and correlated this with survival data (28).

First these authors found it difficult to categorize malignant lymphomas into separate B and T cell groups on a morphologic basis alone. "While the T-cell or B-cell can often be assumed or inferred from certain cytologic features and patterns of growth, there is no conclusive evidence that the number of cases in which this can be done is sufficiently large to make this classification suitable for use in clinical programs" (28). This criticism is further supported by the recent NCI study in which 37% of routinely stained lymphomas were found to be unclassifiable by the Lukes-Collins classification (compared to 15-30% for the other classifications) (24). A third study by Jaffe et.al. has similarly found difficulty in predicting immunologic phenotype by morphologic criteria alone (44). These authors were only able to correctly predict immunologic phenotype in 61% of 29 cases of diffuse aggressive Non-Hodgkin's lymphomas.

The second criticism stated in this paper concerns the "U-cell" class proposed by Lukes and Collins. The U-cell category, they claim, is difficult

to comprehend or elucidate. If the U-cell is defined by lack of surface marker then it becomes a heterogeneous group that can have little predictive value, and thus Lukes and Collins have introduced a term which is at best, ambiguous. They claim that more than thirty percent of histiocytic lymphomas do not have cell markers and would thus be classified as U-cell. In addition, they claim that, since in rare cases any morphologic type of NHL may lack surface markers, there is no consistent correlation between morphology and immunology in the U-cell category (28).

Another major criticism that has been cited against the Lukes-Collins classification is the lack of emphasis placed upon the architectural pattern of the lymphomas. Nathwani et al separated their cases by both Lukes-Collins classification as well as by architecture and compared survival times. What they found was that within each Lukes-Collins class, nodular architecture conferred a better prognosis. Thus, they claim that even if nodularity has no conceptual relevance it does provide prognostic information and should be included in any classification scheme (28). This conclusion is supported more recently in the National Cancer Institute study of the classifications of the NHL which will be discussed later. This study too showed an association between nodularity and survival independent of cell type (24).

Nathwani has also criticized the Lukes-Collins classification by stating that they found no apparent significance in dividing the histiocytic lymphomas of Rappaport into five categories. They did find that the large cleaved FCC lymphomas did better, but found no difference among the rest. In addition, they claimed that it was difficult to separate this group by morphology alone and thus question its ultimate usefulness. Recently however, a study by

Van der Valk et. al. (39) investigated this problem and concluded that by using morphometric cell parameters alone, including nuclear size and shape, cytoplasm area, and cytoplasm to nucleus ratio, it was possible to separate the large non-cleaved FCC lymphomas from the immunoblastic sarcomas and from "true" histiocytic lymphomas.

In the most recent paper by Nathwani et. al. (64) the authors did not specifically comment on the difficulty they encountered subdividing the DHL by the Lukes-Collins classification. However, 59 out of 279 (21%) cases were found to be of suboptimal technical quality for precise subcalssifications. Of the cases used in the study a consensus was reached regarding subclassification in 129 of 162 (80%). This corresponds with other studies (23,37) which reported on the reproducibility of the Lukes-Collins classification. No significant difference in survival was found, using these 162 cases, between any of the 5 Lukes-Collins subdivisions of diffuse histiocytic lymphoma.

Other Classifications

Dorfman Classification: Proposed first in 1974, the Dorfman classification is a compromise between the Rappaport, Lukes-Collins, and the BNLI classifications and represents an attempt to eliminate controversial terminology, such as "histiocyte". Like that of Rappaport, the Dorfman classification makes a distinction on the basis of architecture and does not use B and T cell terminology (40).

BNLI Classification: Proposed in 1973, the BNLI classification is essentially a modification of the Rappaport system that recognized the follicular center origin of nodular lymphomas. It separates the NHL also into two grades: Grade I, with a better prognosis, comprised of the nodular lymphomas and the more well-differentiated ones, and Grade II, comprised of the histiocytic lymphomas and those that are poorly differentiated (41).

WHO Classification: The classificaton of the World Health Organization is acknowledged as a compromise based on our current limited understanding of the lymphomas. It is "...subject to further modification as new knowledge accumulates on the precise origin of the tumor cells" (42). This classification groups the NHL by architecture.

Kiel Classification: Proposed by Lennert and his collaborators, the Kiel classification is widely used in Europe. This system does not separate by B or T cell origin, but uses the words "centrocyte" and "centroblast" to refer to what Lukes and Collins call "cleaved" and "non-cleaved" cells respectively. The Kiel classification groups the NHL by two grades of malignancy: High and Low (43).

The NCI Sponsored Study of the Classifications of the Non-Hodgkin's Lymphomas

It should now be apparent how this explosion of "definitive" classifications, while indeed providing useful information and fuel for debate, was able to confuse even the most dedicated physician. With at least six major classificatons (and just as many minor ones) it became difficult for the average physician to interpret the literature on the NHL and compare studies done at different centers using different classification.

In 1981 the NCI sponsored a study in an attempt to eliminate some of this confusion. Taking pathologic material from 1175 cases of NHL, slides were presented to each of six "experts" who were proponents of one of the major classifications. The slides were also presented to six "experienced" pathologists not connected to a particular classification. Each pathologist reviewed each slide using ordinary H & E stains and gave his or her diagnosis. The "experts" used the classification scheme they were the proponent of, while the "experienced" pathologists classified each slide by each of the classifications. Slides were also resubmitted to each pathologist to test reliability. The diagnoses were then correlated with clinical information from each case.

The major conclusion of the study (much to the relief of the "experts") was that "...all six classifications were valuable and comparable in reproducibility and clinical correlations." In addition, it was concluded that each system separated the patients into subgroups with varying prognoses, from good to poor, and no system was superior to any other in this regard. This study also confirmed previous observations that those lymphomas which display a nodular (follicular) architecture have a better prognosis than those with a

diffuse architecture. Finally, from the work done in this study, a "working formulation" for the classification of the NHL was proposed which, using morphologic criteria alone, subdivides the NHL into ten groups. Sub-classifications are provided as a means by which translation can be made between each of the six major systems to facilitate comparison of clinical reports and therapeutic trials. This working formulation is presented in Table 6. This formulation makes no provision for B or T cell categories.

Summary of Classification Systems

It should be clear by now that the search for an easy, reproducible, scientifically accurate, and prognostically relevant classification scheme for the NHL is far from over. The Rappaport system has been proven to be prognostically significant but appears scientifically out-moded. The Lukes-Collins classificaton, while including the latest in immunologic research, appears difficult to use at the present time. The "working formulation" developed by the NCI is a worthwhile attempt to provide a "universal translator" but since it does not include T or B cell terminology it appears already "old fashioned".

The search for the "definitive" classification scheme will progress while our knowledge of immunology moves forward. Ultimately a more ideal understanding of normal lymphocytes and lymphomatous cells will allow us to reclassify the lymphomas so that we will be able to design therapy on a purely biologic basis.

Table 6. WORKING FORMULATION OF NCI STUDY OF NHL CLASSIFICATION

LOW GRADE

A. Small Lymphocytic
   - consistent with CLL
   - plasmacytoid
B. Follicular, small cleaved cells
   - diffuse areas
   - sclerosis
C. Follicular, mixed small and large cell
   - diffuse areas
   - sclerosis

INTERMEDIATE GRADE

D. Follicular, large cell
   - diffuse areas
   - sclerosis
E. Diffuse, small cleaved cells
   - sclerosis
F. Diffuse, mixed small and large cell
   - sclerosis
   - epithelioid cell component
G. Diffuse, large cell
   - cleaved cell
   - non-cleaved cell
   - sclerosis

HIGH GRADE

H. Large Cell, immunoblastic
   - plasmacytoid
   - clear cell
   - polymorphous
   - epithelioid cell component
I. Lymphoblastic
   - convoluted
   - non-convoluted
J. Small Non-cleaved Cell
   - Burkitt's
   - follicular areas

Miscellaneous
Composite
Mycosis Fungoides
Histiocytic
Extramedullary plasmacytoma
Unclassifiable

(Adapted from NCI study of classifications of NHL (24))

DIFFUSE HISTIOCYTIC LYMPHOMA

Diffuse Histiocytic Lymphoma (DHL) is one of the most common subtypes of the Rappaport classification of the NHL, comprising about one third of all non-Hodgkin's lymphomas. Since it was originally described by Rappaport, DHL gained the reputation as being a highly aggressive neoplasm that was refractory to treatment (46). However, over the last fifteen years great advances have been made in its treatment, especially in the area of combination chemotherapy, so that it is now considered a "potentially curable" neoplasm (47). It has been demonstrated that in actuality DHL is comprised of a group of neoplasms with widely divergent histology, natural history, and response to treatment. Complete response rates up to 69% have been achieved (48) but there remains a large group that has proven to be unresponsive to treatment. Many attempts have been made to identify this sub-group in advance of treatment and investigation continues to develop aggressive treatment for it. The study which follows is one such attempt. Before the study is presented prognostic factors in DHL will be discussed followed by a review of current treatments for the disease.

Prognostic Factors in DHL

Site of Involvement: Numerous studies have discussed site of primary involvement as a prognostic factor in DHL. However no consistent conclusion can be drawn from these studies. A retrospective review by Fisher et. al. (49) identified gastrointestinal involvement and hepatic involvement as predictors

of a poor prognosis for patients with diffuse histiocytic, mixed, or undifferentiated lymphomas. Other studies however have discounted GI or liver involvement (50,51) as a poor prognostic factor. Presence of a "huge" GI tumor (10 cm), and involvement of the CNS have similarly been correlated with poor prognosis but there appears to be no consensus on this issue (36, 49-53). A study by Strauchen (36) indicated a high correlation between immunoblastic sarcomas and CNS and GI involvement which might account for the occasional finding of poor survival among patients with involvement at these sites. Invasion of the bone marrow seems to be correlated with poor prognosis and this is supported by a number of studies (49-53).

Laboratory studies: There is some indication that serum LDH > 250 u/liter is a predictor of poor survival (49) although some authors have suggested that levels above 500 U/liter are more significant (50). A hemoglobin level of less that 12 mg/ml was identified as a predictor of poor prognosis in one recent study (51). This study also found no correlation between Erythrocyte Sedimentation Rate and prognosis.

Age/Sex: Again the literature presents a mixed picture but age and sex do not seem to be correlated with survival. However one study found that male sex was a poor prognostic factor (49) while another found that age greater than 60 years was correlated with poor survival (51).

Stage: Staging of the NHL in general, and DHL in particular, has not proven to be as clinically useful as it has in Hodgkin's disease. Theoretically, Rosenberg (54) has suggested, a staging system should 1) provide prognostic information, 2) assist the physician in selecting therapy, 3) provide a standardized system for international comparisons, and 4) describe

the extent of the disease. The Ann Arbor scheme for the staging of Hodgkin's disease (see Table 7) has been applied to the NHL and has fulfilled the last three of these goals. It has not however, supplied much in the way of prognostic information. For example a patient with nodular poorly-differentiated lymphocytic lymphoma may present with stage IV disease but may run an indolent course, while a patient with DHL may have a much poorer prognosis even though he/she may present with stage II disease. It has been suggested that clinicians use a sequential staging scheme based on the Ann Arbor staging system while being aware that other factors weigh more heavily in the determination of prognosis (55). (See Table 8).

Pathology: Most studies have indicated that the single most important factor in determining prognosis is pathological classification. As it has already been discussed, in the Rappaport classification, a good prognosis is indicated by a nodular lymphoma or one composed of lymphocytes. However the Rappaport classification make no attempt to separate lymphomas of the diffuse histiocytic type into different groups. The Lukes-Collins classification divides the DHL into five categories which have been discussed. There appears to be some difference among these five groups in terms of prognosis but this is still a controversial point.

Table 7. ANN ARBOR STAGING CLASSIFICATION

Stage I
Involvement of a single lymph node region (I) or localized involvement of a single extranodal organ/site (Ie).

Stage II
Involvement of more than one lymph node region on the same side of the diaphragm (II) or of one or more lymph node regions and localized involvement of an extralymphatic organ/site (IIe) on the same side of the diaphragm.

Stage III
Involvement of lymph node regions on both sides of the diaphragm (III) which may be accompanied by involvement of the spleen (IIIs) or by localized involvement of an extralymphatic organ/site (IIIe) or both (IIIse).

Stage IV
Diffuse or disseminated involvement of one or more extra-lymphatic organ/site with or without lymph node involvement.

Table 8. SEQUENTIAL STAGING OF NHL

Complete history and physical examination
Routine hematology and chemistries
Standard chest radiography
Metastatic skeletal survey
Isotopic bone/liver-spleen scanning
Bipedal lymphangiography
Bone marrow biopsy
Percutaneous liver biopsy
Liver biopsies via peritoneoscopy
Staging laparotomy

(From Chabner et. al. (55))

Treatment of Diffuse Histiocytic Lymphoma

Treatment of localized DHL

Approximately 20-30% of patients with DHL present with localized (Stage I or II) disease. Sweet and Golumb have recently reviewed their experience with radiation therapy in localized DHL. Treating 28 patients with stage I or II disease they found that patients with stage I disease achieved a median survival of 72.5 months and a 93% 11 yr. actuarial disease free survival. Patients with stage II disease fared much worse with a median survival of 33 months and an 11 yr. actuarial survival of 33%. Many centers now treat stage I disease with radiation therapy alone and treat stage II with adjuvant chemotherapy or chemotherapy alone (56).

Treatment of advanced DHL

The treatment of advanced DHL (stages II-IV) has changed considerably in the last decade. Far from the aggressive neoplasm which carried a uniformly poor prognosis, DHL is now considered a "potentially curable" neoplasm. Single agent chemotherapy in the sixties was disappointing, producing few complete remissions, with 5-10% of patients achieving a complete remission and median survival averaging less than one year. Treatment with CVP (cyclophosphamide, vincristine, and prednisone) increased the complete remission rate but did not affect survival (48). In the early seventies aggressive combination chemotherapy was found to be successful in patients with Hodgkin's disease

(nitrogen mustard, vincristine, procarbazine, and prednisone) and using cyclophosphamide in place of nitrogen mustard DeVita achieved a complete remission rate, for patients with DHL, of a rather low 50% but found that this remission was very durable, 91% of the complete responders remaining disease free for 26-105 months (47). In 1972 and 1975, researchers at Yale, using a regimen called COMA (cyclophosphamide, vincristine, methotrexate with leucovorin, and cytosine arabinoside) reported similar durable remissions in 6/8 patients (57).

Since the advent of the newer antitumor antibiotics, adriamycin and bleomycin, numerous regimens testing the efficacy of these drugs have been devised. The trials of these newer combinations have been numerous and the details of each are beyond the scope of this paper. Sweet and Golomb have reviewed the current status of the combination chemotherapy of DHL (48). A table giving the results of some of these studies can be seen in Table 9. It has proven difficult to compare the results of these studies for a number of reasons. First of all, even though the acronyms used in different studies may be the same, the dosage and administration schedules are often different. Second, there are often differences in restaging techniques done after achievement of a complete remission so that the meaning of remission may vary from one study to another. In addition, some studies use maintenance chemotherapy in addition to the initial therapy while others do not. Finally the number of patients in each study is often small making statistical significance difficult to achieve.

Since the review by Sweet and Golumb, two new combinations of standard chemotherapeutic agents have been published. Laurence et. al. (58) have

reported the results of a study of a six-drug chemotherapy regimen called COP-BLAM (cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin and procarbazine) administered to patients with stage III and IV DHL. They achieved a complete remission rate of 73% and partial response rate of 24%. Median survival has not yet been reached. Ginsberg et. al. (59) recently reported a trial of cyclophosphamide, doxorubicin, vincristine combined with continuous infusion of low-dose bleomycin. The rationale for the continuous infusion of bleomycin, rather than the bolus administration found in other regimens, was an attempt to reduce pulmonary toxicity while keeping a steady state therapeutic level of bleomycin. Complete remission rate from this study was 77% for DHL patients who had had no prior chemotherapy while no patient in the study developed pulmonary toxicity (n=37).

A few conclusions are possible from the data generated at the various centers; 1) There are numerous chemotherapeutic regimens that are successful in achieving complete remission in DHL, 2) remission rates vary between 41-69%, 3) regimens using maintenance therapy have not produced more durable remissions than those without maintenance therapy, 4) cures appear to be possible only after the achievement of a complete remission and patients remaining in remission for two years appear to be cured of their disease (48).

Table 9. A COMPARISON OF CHEMOTHERAPEUTIC TREATMENT OF ADVANCED DHL

Regimen	Complete response rate %	50% survival	Comments
COMA	75%	--	selected series
C-MOPP	41%	9	restaged; few relapses after 2 yrs if CR
BACOP(NCI)	48%	14	selected series
CHOP/HOP	68%/66%	23	+maintenance
BACOP(Farber)	56%	9	+maintenance
COMA	40%	9	selected series
CHOP ± Bleo	61%	25(approx)	some with BCG
COMLA	55%	+25	unselected
COP-BLAM	73%	+26	50% survival not reached yet

C = Cyclophosphamide
O = Vincristine
M = Methotrexate (ex C-MOPP where M=Nitrogen mustard)
A = Cytosine arabinoside (ex COP-BLAM where A=Adriamycin)
P = Prednisone
PP = Prednisone + Procarbazine
B = Bleomycin (also BL)
H = Adriamycin
L = Leucovorin rescue

(adapted from Sweet and Golomb (48))

A RANDOMIZED TRIAL OF ACOMLA AND CHOP-BLEO IN ADVANCED DHL

Introduction to Study

A randomized trial of two chemotherapy treatments was initiated in 1975 with two main goals. The first was to compare the efficacy of a new regimen ACOMLA to that of a commonly used drug combination CHOP-Bleo (descriptions below) for the treatment of advanced DHL. The second goal was to see if the Lukes-Collins classification was able to identify subsets of DHL that were unresponsive to treatment so that these subsets could be identified prospectively and more aggressive treatments designed for them.

Individual Chemotherapeutic Agents

Cyclophosphamide (Cytoxan) is an alkylating agent that acts by inactivating DNA, which may be administered both intravenously or orally. It is not cell cycle specific and causes most of its toxicity during the S-phase. Bone marrow suppression is common and is the limiting toxicity. Nausea, vomiting and alopecia are common (60).

Doxorubicin (Adriamycin) is an anthracycline antibiotic which binds DNA permitting intercalation thus impairing the template activity of the DNA. The drug may only be given intravenously. Myelotoxicity is the major complication and nausea, vomiting and alopecia are common. Tissue necrosis can occur if the drug extravasates during administration. This drug causes an unusual form of cardiomyopathy which may be fatal, although death is rare with total dosage of less than 500 mg/m2 (60).

Vincristine (Oncovin) is a derivative of an alkaloid found in the periwinkle Vinca rosea. Its mechanism of action is not clearly defined but it is thought to inhibit the cell cycle at metaphase by damaging spindle protein. It is only administered intravenously and does not cause myelosuppression. Neurotoxicity is common and reversible paresthesias may occur (60).

Methotrexate is a folate antagonist that acts by inhibiting the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. The result of this is inhibition of DNA synthesis. It is cell cycle specific and causes cell death during the S-phase. Leucovorin (folinic acid) is administered after high or intermediate dose methotrexate to decrease toxicity. Toxicity includes renal crystal formation, myleosuppression, nausea, vomiting and vasculitis (60).

Cytosine Arabinoside (Cytarabine, Ara-C) is an analogue of deoxycytidine that has a structural alteration in the sugar moiety and acts by inhibiting DNA polymerase. It is cell cycle specific acting during the S-phase. Its major toxicity is myelosuppression (60).

Bleomycin is an agent isloated from Streptomyces verticillus which kills dividing cells by causing chain fragmentation of DNA. It is administered intravenously. Its most common toxicity is pulmonary fibrosis which generally occurs at doses over 400 units. The development of diffuse interstitial fibrosis can be anticipated by a decrease in diffusing capacity (60).

Prednisone is a corticosteroid which acts on neoplastic cells by an unknown mechanism. Side effects include GI bleeding, electrolyte imbalances, and alterations in the psyche (60).

The Therapeutic Regimens

The two chemotherapeutic regimens used in this study are called CHOP-Bleo and ACOMLA. CHOP-Bleo has been used since 1972 and has been reported to result in a complete remission rate of 65% (61). It utilizes cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone and bleomycin. The ACOMLA regimen evolved from COMLA with the addition of hydroxydaunorubicin. COMLA was used by Sweet et. al. and is reported to yield a complete remission rate of 55% (52). COMLA was developed to utilize the established agents cyclophosphamide and vincristine for tumor lysis which was then followed by methotrexate and cytosine arabinoside, which kills cells that are synthesizing DNA, for maximum cell kill during the period of rapid growth. In addition, methotrexate and cytosine arabinoside have been shown to act synergistically by enhancing intracellular accumulation of the latter (62). The latter two agents also cross the blood-brain barrier which might help prevent CNS relapses (63).

Materials and Methods

Between May 1976 and April 1982 patients were entered into Yale Human Investigations Committee protocol #1257 (approved May 26, 1976). Conditions required for entry were:

1) A diagnosis of diffuse histiocytic lymphoma (Rappaport)
2) Slides of original biopsy material available for review at Yale
3) Stage III or IV disease (Ann Arbor classification)

4) No previous chemotherapy

5) Measurable disease (by physical exam or otherwise)

6) Granulocyte count greater than 500 cells/mm3

7) Platelet count greater than 50,000/mm3

8) Age greater than 16 years (no upper limit)

9) Ability to give informed consent

Patients were not excluded with prior radiotherapy (unless this included all sites known to have disease), poor Karnovsky status, or concurrent medical illnesses.

All patients received the following evaluation:

1) Complete history and physical examination

2) Complete blood count, liver and renal function tests

3) Chest X-ray

4) Bilateral (iliac crest) bone marrow biopsy (with aspiration if possible)

5) Lymphangiography with intravenous pyelogram

6) Gallium scan

7) Liver-spleen scan

8) Abdominal ultrasound, CT scan, GI series (if GI involvement or GI symptoms)

9) Lumbar puncture for cytology (if bone marrow involved)

10) MUGA scan (if at risk for adriamycin cardiotoxicity)

11) Pulmonary function tests (if at risk for pulmonary toxicity)

In addition, original slides of biopsy material were reviewed blindly and classified according to the Lukes-Collins classification.

Each patient was randomly (by coin-toss) assigned to either the CHOP-B or ACOMLA treatment arms. These treatments consisted of:

ACOMLA:	Adriamycin	40 mg/m^2	IV	Day 1
	Cyclophosphamide	1 g/m^2	IV	Day 1
3 CYCLES	Vincristine	2 mg	IV	Days 1,8,15
	Methotrexate	120 mg/m^2	IV	
	Leucovorin	25 mg q6hx6	PO	Days 22,29,36,43, 50,57,71
	Cytosine arabinoside	300 mg/m^2	IV	
CHOP-Bleo:	Adriamycin	40 mg/m^2	IV	Day 1
	Cyclophosphamide	1 mg/m^2	IV	Day 1
9 CYCLES	Vincristine	2 mg	IV	Days 1,5
	Bleomycin	15 Units	IV	Days 1,5
	Prednisone	100 mg/m^2	PO	Days 1,5

Each treatment lasted nine months (3 cycles of ACOMLA or 9 cycles of CHOP-B). Additional cycles were used when there was a question of persistent disease. Patients at risk for the toxic effects of chemotherapy were identified and treatment was reduced. These patients were identified by 1) increased age, 2) extensive radiotherapy or bone-marrow involvement, 3) elevated bilirubin, 4) history of heart failure or arrythmias, 5) poor

pulmonary function. Dosages were modified according to Table 10, for decreased granulocyte count, nausea and vomiting, pulmonary fibrosis, diabetes mellitus, history of psychosis, paresthesias, and muscle weakness.

One month after completion of therapy all patients were restaged using the same procedures described in the initial evaluation. If previous sites of disease had clinical evidence of continued disease these sites were re-biopsied. Patients were then followed at two month intervals for two years then followed at six month intervals. A complete response (CR) was defined as total disappearance of disease for one month after chemotherapy. A partial response (PR) was defined as a reduction in tumor size of at least 50% for at least one month. Any response less than this was considered a non-response (NR). Patients who failed to respond at all to chemotherapy were considered indiction failures. These were included in statistical analysis as non-responders.

Survival was calculated from the date of protocol entry. Freedom from relapse was calculated from the date of objective CR to date of documented relapse or date patient was last seen and known to have continued in CR after reevaluation. Most patients obtaining CR did so within two months of initiation of therapy. To eliminate observer subjectivity, freedom from relapse was also calculated for those acieving CR from the date therapy ended to the same end point as previously mentioned. This calculation was used unless otherwise stated. Survival was correlated with certain factors that have been associated with prognosis. These were: age, sex, size of mass, presence of bone marrow involvement, CNS involvement, GI involvement, and Lukes-Collins pathology. Survival curves were calculated and compared using the Wilcoxon test.

Table 10. DOSE MODIFICATIONS

1. Hematologic

   a. Regimen A

      i. Decrease adriamycin and cyclophosphamide by 1/3 if the nadir granulocyte count achieved is less than 300/mm3

      ii. Decrease MTX and cytosine arabinoside by 1/3 if WBC, at time of treatment, is 2,500 to 3,500/mm3. Omit dose if WBC is less than 2,500/mm3

      iii. Decrease MTX by 40mg/m2 increments if WBC $<$ 4,000/mm3 prior to dose.

   b. Regimen B

      i. Decrease adriamycin and cyclophosphamide dose by 1/3 if nadir granulocyte count after previous dose is less than 300/mm3.

      ii. Wait 1 week if WBC $<$ 3,000/mm3 at 3 weeks.

2. Other

   a. Cytosine Arabinoside - decrease to 100mg/m2 for protracted unmanageable nausea and vomiting.

   b. Adramycin - limit total accumulative dose to 450mg/m2 (adriamycin + cyclophosphamide increases cardiotoxicity) Omit if bilirubin $>$ 3mg%.

   c. Bleomycin - limit total accumulative dose to 300mg <u>total</u> (Pulmonary fibrosis occurs occasionally after this dose)

   d. Prednisone - omit if ulcer history or symptoms. Omit if diabetes mellitus or history of psychosis.

   e. Vincristine - reduce 50% for severe paresthesias or unmanageable constipation. Omit for profound muscle weakness, foot drop or ileus. Give only 1 mg total dose for age $>$ 65 yrs.

   f. Methotrexate - do not escalate as outlined above if WBC not $>$ 4,000/mm3. Do not escalate if mucositis present.

Results

During the study period, between May, 1976 and April, 1982, a total of 54 patients were entered into the protocol. Of these, 4 were omitted from analysis on pathology review, having lymphomas other than the diffuse histiocytic type. Another two were omitted because on review they were found to have only stage I or II disease. Of the remaining 48, two did not have a Lukes-Collins classification specified at the time of review so they were omitted from this part of the analysis. Tables 11 and 12 show the general characteristics of the patient population. The median age for all patients was 58.4 and the sex ratio was 28:20, with females predominating.

Table 11. CLINICAL CHARACTERISTICS BY LUKES-COLLINS PATHOLOGY

		STAGE			SITES			MASS	REMISSIONS			Rx	
Lukes-Collins	#	III	IV	Sx	BM	GI	CNS	>10cm	CR	PR	NR	A	C
lclFCC	13	4	9	4	4	1	0	1	8	4	0	6	7
lncFCC	7	2	5	2	0	2	0	3	6	0	1	0	7
B-IBS	14	5	8	4	3	5	0	4	8	3	3	6	8
T-IBS	8	4	4	4	2	1	0	1	5	2	1	5	3
LCU	4	1	3	0	0	0	0	1	4	0	0	3	1

lclFCC = large cleaved FCC
lncFCC = large non-cleaved FCC
B-IBS = B Cell immunoblastic sarcoma
T-IBS = T Cell immunoblastic sarcoma
LCU = large cell unclassified

Rx A = ACOMLA
Rx C = CHOP-B
Sx = "B" symptoms

Table 12. CLINICAL CHARACTERISTICS BY TREATMENT

Rx	AGE	SEX		STAGE		SITES			MASS
	(mean)	M	F	III	IV	BM	GI	CNS	>10cm
ACOMLA	59.1	12	8	4	16	6	3	0	3
CHOP-B	57.8	8	20	13	15	3	7	0	7

ACOMLA vs. CHOP-B

Of the 48 patients, 20 were treated with ACOMLA and 28 were treated with CHOP-B. Of the ACOMLA patients one had not yet been restaged at the time of analysis and, although he was described as being in clinical remission, he was not included in the analysis. Most patients who achieved a complete remission did so during the first two months of therapy. The response rates are listed in Table 13. There was no significant difference in response rates between the two treatments.

Table 13. RESPONSE RATES

Rx	CR	PR	NR
ACOMLA	13/19 (68%)	4/19 (21%)	2/19 (11%)
CHOP-B	20/28 (71%)	5/28 (18%)	3/28 (11%)
TOTAL	33/47 (70%)	9/47 (19%)	5/47 (11%)

Of those patients achieving a complete response there were 7 patients who had a relapse. 4 of these had bee treated with ACOMLA and 3 with CHOP-B. The time to relapse ranged from 2 months to 32 months (mean 10 months) with no significant difference between the two treatment arms. Of those patients with a CR, 6 have died. Four of these died after a relapse with progression of their disease (2 ACOMLA, 2 CHOP-B). The other two deaths were apparently

unrelated to their lymphoma. One died a sudden death 8 months after therapy while the other died with a pneumonia 14 months after therapy.

The median survival for all patients has not yet been reached. The median follow-up time is 32 months (37 for ACOMLA patients, 29 for CHOP-B patients). Of those patients who did not respond to therapy the median survival time was less than 6 months. Of those patients who obtained only a partial response, 5 are alive on various chemotherapeutic agents while the median survival of the other 4 was 12 months.

Drug toxicity was substantial. There were three drug-related deaths (2 ACOMLA, 1 CHOP-B). Two patients developed bleomycin toxicity demonstrated by a decrease in pulmonary function tests. Three patients developed adriamycin cardiotoxicity (1 ACOMLA, 2 CHOP-B). Six patients developed neurotoxicity from the vincristine (1 ACOMLA, 5 CHOP-B). There was a small difference in sepsis between the two treatment arms with 37% of ACOMLA patients and 18% of CHOP-B patients having treatment-related sepsis. This difference was not significant ($p=0.17$).

Prognostic factors

There was no correlation between the patients age, stage, symptoms, sex, GI tract involvement, or tumor size, and survival that proved to be statistically significant. There was, however, a trend for older patients to do poorly, but again, not in a statistically significant manner. For reasons that are not clear there were more females "randomized" to the CHOP-B treatment arm and more stage IV patients to the ACOMLA treatment arm. These differences were

significant. However, since neither age nor stage were correlated with survival, this had no effect on the study. No patients in the study had involvement of the CNS so this could not be analyzed as a prognostic factor.

Nine patients (19%) presented with bone marrow involvement. While this does not adversely affect survival in a statistically significant manner, it should be noted that only one of these patients has achieved a documented complete remission and this patient had a relapse two months after completion of therapy. Another is in clinical remission but has not been restaged. The others achieved a partial remission. It is interesting to note that the two patients with bone marrow involvement who attained a CR had been treated with ACOMLA. In view of the small numbers involved it would be unwarranted to draw any conclusions from this.

Table 10 shows the distribution of patients by Lukes-Collins pathology. For analysis, patients were grouped into immunoblastic sarcomas (T and B cell types) and "others" (lclFCC, lncFCC, and large cell unclassified). There was a decrease in survival for patients with immunoblastic sarcomas ($p=0.01$) but there was no difference in relapse free survival. There was no difference between the FCC cleaved and non-cleaved types with regards to survival.

There were four cases of patients with second malignancies: squamous cell carcinoma of the lung, carcinoma of the prostate, acute myelogenous leukemia, and grade I transitional cell cancer of the bladder. The first two were found in patients treated with CHOP-B within one year of attaining CR. The patient with AML was diagnosed one month after completion of ACOMLA. The case of bladder cancer was diagnosed at the same time as the lymphoma as was treated with excision.

Discussion

This study was originally designed for two reasons. The first was to compare the new regimen ACOMLA with CHOP-B in the treatment of advanced diffuse histiocytic lymphoma. The second was to identify factors (eg. Lukes-Collins classification) that would be useful in defining that subset of DHL with a poor prognosis and refractory to treatment.

As was mentioned in the section on "treatment" the ACOMLA regimen evolved for several theoretical reasons. The anti-metabolites methotrexate and cytosine arabinoside are given after tumor lysis to insure maximum cell kill during the period of rebound growth. Administration of cytosine arabinoside after methotrexate has been shown to increase its intracellular concentration. In addition, these two drugs have been shown to cross the blood-brain barrier and thus, it is supposed, might help to prevent CNS relapses which have proven to be problematic in other studies (65).

The results of this study indicate that there is no difference in outcome between either treatment, measured by response rates and survival. There is a trend (not significant) toward greater toxicity with ACOMLA. The question of whether or not ACOMLA was useful in preventing CNS relapses was not answered by this study. There were only 9 patients who were at risk for a CNS relapse (with bone marrow involvement) and only one of these attained a documented complete remission. It is interesting to note that in patients who had bone marrow involvement and thus were at risk for CNS relapse, the dosage of cyclophosphamide and adriamycin was reduced by 33% (by protocol) to avoid dangerous bone marrow suppression. It may be that with these patients the risk of bone

marrow toxicity may have to be balanced against the desire to attain a complete remission and the dosage should not be reduced.

There appears, then, at this time, no reason to recommend ACOMLA over CHOP-B. CHOP-B is cheaper ($2700 for CHOP-B, $3700 for ACOMLA), easier to give, and has a slightly lower rate of toxicity, but ACOMLA may prove to be more effective for patients with marrow involvement and uses a lower total dosage of adriamycin.

The results of this study indicate that GI involvement, tumor size, age, sex, stage, or presence of symptoms, were not useful in identifying that subset of patients with a poor prognosis. This is in agreement with data from some centers but is in disagreement with others. There is no apparent explanation for this difference. Hematocrit and serum LDH levels were correlated with prognosis in one study but were not included in the present one. There was a trend for patients with bone marrow involvement to have difficulty in attaining a complete remission and the one patient with a documented CR had a relapse two months later. The number of patients with bone marrow involvement were small, however, and this was not a statistically significant finding.

The ability of the Lukes-Collins classification to identify subsets of DHL with varying prognoses is currently a controversial subject. As was discussed above, some studies find that the large-cell FCC lymphomas have a better prognosis than the immunoblastic sarcomas, while others dispute this finding. Some studies have shown the large cleaved FCC lymphoma to have a better prognosis than the large non-cleaved variety, while one study reports the opposite. Still other studies have indicated no significant differences in survival between any of the large cell lymphomas.

It is difficult to explain why this controversy exists in the literature. There have been few studies that are prospective randomized trials with the patients given uniform treatment. Sample sizes are small which makes it difficult to compare results from different centers. In addition, there is the apparent difficulty in using the Lukes-Collins classification which may result in slight variances in interpretation of the histologic subclassifications. there does seem, however, to be a distinct trend for the FCC lymphomas to have a better prognosis than the immunoblastic sarcomas. The results of this current series supports this conclusion. There was no difference found between the cleaved and non-cleaved FCC lymphomas. It is important to note that the relapse-free survival for the FCC and immunoblastic lymphomas was the same. What this indicates is that once a patient achieves a complete remission his/her survival is independent of histology. Thus it is apparent that the Lukes-Collins classification does indeed identify a subset of DHL that carries a poor prognosis and is refractory to current treatment. It can be inferred from this that a more efficacious treatment should be designed for these patients in order to induce a complete remission and thus increase their survival.

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